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09/807,402	08/03/2001	Peter Hofert	SCH 1808	9208
23599	7590	08/11/2006		
MILLEN, WHITE, ZELANO & BRANIGAN, P.C. 2200 CLARENDON BLVD. SUITE 1400 ARLINGTON, VA 22201			EXAMINER MAIER, LEIGH C	
			ART UNIT 1623	PAPER NUMBER

DATE MAILED: 08/11/2006

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**MAILED**  
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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 09/807,402

Filing Date: August 03, 2001

Appellant(s): HOFERT ET AL.

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Csaba Henter  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed June 5, 2006 appealing from the Office action mailed September 1, 2005.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The Appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The Appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

WO 96/20209	Schollkopf et al	7-1996
5,798,338	Backensfeld et al	8-1998

Hedges, A. "Industrial Applications of Cyclodextrins" Chem. Rev. vol 98, (1998) pp 2035-2044.

**(9) Grounds of Rejection**

The following grounds of rejection are applicable to the appealed claims:

Claims 2-5, 7, 10, 11, 13-16, 18-20, 22, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schollkopf et al (WO 96/20209) and Backensfeld et al (US 5,798,338) in view of Hedges (Chem. Rev., 1998).

The invention is drawn to a combination, including a pharmaceutical composition, comprising a gestagen of Formula I with a cyclodextrin. Dependent recite species of gestagens and CDs and ratios of the components and methods of preparing the combination.

Schollkopf teaches the gestagens of Formula I. See col 1-4. The species recited in claims 3 and 20 is disclosed at p. 6. The reference further teaches that the disclosed compounds have high activity and can be used in low dosages, alone or in combination with estrogens to prepare compositions having utility as oral contraceptives. The reference also suggests the addition of solubilizers to enhance solubility of the compounds. See pages 8 and 9.

The reference does not teach the combination of gestagens with CDs or methods of preparing such a combination.

Backensfeld teaches the preparation of solid dosages of sex hormones but notes drawbacks in such preparations, such as the reduction of the active ingredient due to oxidative degradation. See col 1, lines 1-27. The disadvantages of such dosage forms apply to sex hormones in general, including estrogens and gestagens. See col 1, lines 34-49. The reference teaches that such drawbacks can be reduced or avoided by preparing CD clathrates of the active ingredient hormone(s)—that is, the active ingredients would be stabilized with respect to oxidative degradation. See col 1, lines 28-33. The reference further suggests CD species, ratios of the components, and methods or preparing compositions. See col 2, lines 8-62. The reference does not describe a process as “trituration,” but the described process of kneading the components would be essentially the same as trituration. The examples exemplify adding an ethanolic solution of the steroidal hormone to an aqueous solution of CD to form a complex (co-crystallization) and pressing said complex into tablets. See examples 1-4.

Methods for preparing CD complexes with small molecules are well known in the art. Hedges teaches several methods. See Section I, pp 2025-6. Hedges also notes that CDs are well known for solubilizing and stabilizing pharmaceutical products. See Table 1 and page 2038, 1st full paragraph.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare CD complexes of the gestagens of Formula I in the form of oral dosages for their art-disclosed utility. The artisan would be motivated to prepare such a complex in order to reduce oxidative degradation that is known to occur in steroidal sex hormones and to

increase solubility of the steroidal agents. The artisan would be particularly motivated to select any specific embodiment disclosed by Schollkopf. It would be within the scope of the artisan to select any appropriate CD and ratio of components through routine experimentation. It would be further obvious to use such a product as an oral contraceptive because Schollkopf had taught this utility.

Hedges has established that preparation of such complexes by a number of methods is routine, so in the absence of unexpected results, it would be within the scope of the artisan to select any known method of preparation and further to pelletize the prepared complexes into tablets.

#### **(10) Response to Argument**

Appellant first argues that the “gestagens of Backenfeld et al. are different from the claimed gestagens.” However, the reference suggests possible gestagens that would be suitable for combination with cyclodextrins, but the examiner maintains that the reference is a generic one with respect to gestagens and possible oxidative degradation and is in no way limited to the suggested compounds.

Appellant further contends that Backenfeld is drawn the inhibition of oxidative degradation and does not teach that complexation with a cyclodextrin would prevent/reduce degradation via acyloin rearrangement of the 17- $\alpha$ -hydroxyketone side chain of a gestagen. During prosecution, Appellant submitted a declaration demonstrating this preventive effect. As discussed above, Backensfeld had taught the CDs have the capacity to stabilize gestagens. Therefore, the finding is not unexpected. Appellant states that this effect, the prevention of the

acyloin rearrangement “could not have been expected from the teachings of the prior art.” It appears that Appellant has conflated the idea of “expectation” with that of “prediction.” As discussed above, Hedges teaches that cyclodextrins are known for solubilizing and stabilizing pharmaceutical compounds. It is the examiner’s position that one of ordinary skill (without analogous art) may not be able to predict reliably exactly which particular degradative pathways in which particular compounds would be inhibited, the finding that the compounds *are* stabilized is not unexpected. It may not have been *a priori* predictable, but it is not unexpected. If a similar compound were not stabilized with respect to this rearrangement, the fact that the instant compounds are stabilized might be unexpected. Appellant has not set forth any reasoning demonstrating that one of ordinary skill would find this result unexpected. The examiner maintains that the art of record would lead one of ordinary skill to prepare cyclodextrin complexes of the Schollkopf compounds for the prevention of oxidative degradation and increased solubility. The art does not teach the prevention of an acyloin rearrangement, but it appears that Appellant has recognized another advantage that would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious.

Appellant further argues that “[o]ne of ordinary skill in the art prior to even trying to stabilize ZK 187226, would have checked whether ZK 187226 needs to be stabilized.” Appellants note that the fact that this compound, on its own, is stable, so that there would be no motivation to prepare a cyclodextrin complex. However, Appellant also discloses that in combination with excipients the compound does undergo decomposition. Given that the combination of references are drawn to the oral administration of very small doses of the active

agent, (See discussion cited in Backensfeld at col 1, lines 1-27 and Schollkopf at page 8) thus requiring the use of an excipient, one of ordinary skill would base the determination of stability on the results seen in combination with an excipient—the way it would be used in practice.

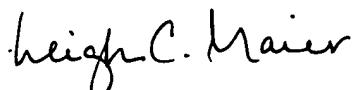
With respect to the particular pathway of degradation, one of ordinary skill performing the tests to determine stability or lack thereof would reasonably expect that, given what was known in the art, this degradation occurs via an oxidative pathway and would therefore be motivated to combine the compound with a cyclodextrin in order to prevent such degradation.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

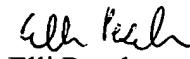
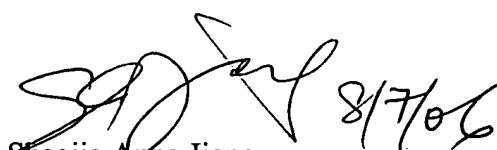
The art of record clearly provides a *prima facie* case for the preparation of the recited complexes of gestagens and cyclodextrins. The results provided in Appellant's declaration are deemed to be results that would not have been predicted, but not unexpected. For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,



Leigh Maier  
Primary Examiner

Conferees:

  
Elli Peselev  
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Supervisory Patent Examiner